DEPARTMENT OF HEALTH AND HUMAN SERVICES

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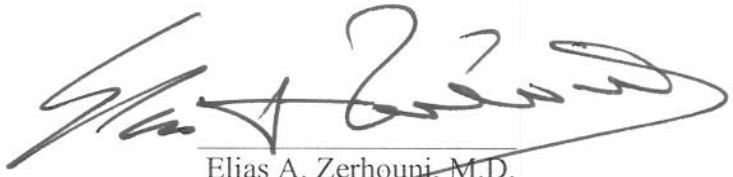
PARKINSON'S DISEASE RESEARCH



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Executive Summary

In their reports for the Fiscal Year 2007 budget for the Department of Health and Human Services (DHHS), the House and Senate Committees on Appropriations requested a report from the NIH outlining an implementation plan for Parkinson's disease (PD) research and a budget that outlines progress already made and results of investments outlined in the 2006 PD Research plan. The following report has been prepared by the National Institutes of Health (NIH), part of the DHHS, in response to this request.

The NIH has been investing in PD research aggressively over the past seven years, and the 2006 PD Research Plan is the most recent in a series of plans that have provided external guidance to the NIH and the PD research community. The current Plan, based on recommendations made at a 2005 workshop that involved scientific and lay representatives, provides goals specifically targeted to therapeutics research. Since the release of this Plan, the NIH has made considerable progress towards many of these goals, including the analysis and public release of large amounts of PD genetic data; the initiation of a large phase III trial of creatine in early-stage PD; the release of grant solicitations on biomarkers of neurodegeneration and drug delivery for neurodegenerative diseases (through the NIH Blueprint for Neuroscience Research); and the development of tools to better assess the non-motor aspects of PD, among many others. Extensive research is also underway in many other areas of PD research, including understanding the environmental risk factors of PD and the basic cell biology of the disease. Lastly, collaborations have been increasing over the past year, highlighted by the cooperation of the patient and practitioner communities, industry, and government to organize the first World Parkinson Congress, held in Washington DC in February 2006.

PD research, like many other research areas, is in a dynamic state as we understand more about what causes PD, how we can best prevent it from occurring in the first place, and/or treat the disease once it is evident. For this reason, our surveillance of the field for new research goals must continue and the NIH is committed to this task. PD remains a high priority for the NIH, and it will continue to be until the research community finds a way to treat PD and its associated conditions more effectively.

PARKINSON'S DISEASE RESEARCH

Introduction

In its report for the Fiscal Year 2007 budget for the Department of Health and Human Services (DHHS; Report No. 109-515) the House Committee on Appropriations stated:

"Parkinson's disease -- The Committee continues to encourage NIH to develop a strategic plan for future investments in PD research, based on the findings of a planning conference tasked with identifying the current shortcomings and future opportunities for more effective treatments and potential cures for the disease, and with a clearly defined budget for achieving those objectives.

The Committee understood last year that NIH convened a conference in June of 2005 and instructed NIH to report back to Congress the conclusions and recommended research plan for the next three years of PD research. The Committee further encourages NIH to submit an implementation plan that outlines progress already made and specific results of investments outlined in that plan by June 30, 2007.

The Committee also encourages continued collaborations including additional intramural activities between NINDS, NIMH, NIA and NHGRI to enhance understanding of neurodegenerative diseases and develop therapeutic applications for gene discoveries." (p. 129)

Similarly, in its report for the Fiscal Year 2007 budget for the DHHS (Report No. 109-287), the Senate Committee on Appropriations stated:

"Parkinson's disease -- The Committee is aware that Parkinson's disease research would benefit from targeted and measured investment of resources by NIH which would result in significant dividends in terms of reduction in human suffering and economic costs to society. Accordingly, the Committee continues to encourage the NIH to develop a strategic plan for future investments in Parkinson's research, based on the findings of a planning conference tasked with identifying the current shortcomings and future opportunities for more effective treatments and potential cures for the disease, and with a clearly defined budget for achieving those objectives.

The Committee understood last year that the NIH convened a conference in June 2005 and instructed NIH to report back to Congress the conclusions and

recommended research plan for the next 3 years of Parkinson's research. The Committee is discouraged that the report was not transmitted to the Committee as requested.

The Committee further encourages the NIH to submit an implementation plan with a research budget that outlines progress already made and specific results of investments outlined in that plan by July 1, 2007." (p. 166)

The following report has been prepared by the National Institutes of Health (NIH), part of the DHHS, in response to these requests.

Background

For several decades, fundamental research supported by the NIH has contributed to important advances in understanding and treating Parkinson's disease (PD). Early studies of levodopa contributed to its use as the mainstay of current drug therapy, and characterization of the brain circuitry affected by PD, the development of primate Parkinson's models, and electrode technology studies were critical in the development of deep brain stimulation (DBS; the delivery of electrical stimulation to specific cellular targets in the brain). In the mid-1990's, technological and scientific breakthroughs opened new opportunities in many areas of the neurosciences. For the PD research community, the NIH-led discovery of alpha-synuclein – the first gene implicated in PD – played an important role in this transformation by providing a starting point to understand what goes wrong at the molecular level. Intracellular accumulation of alpha-synuclein has proven to be a central abnormality common to PD as well as to other related disorders. PD, multiple system atrophy and diffuse Lewy body disease are now considered biologically similar as a family of "synucleinopathies." This raises hope that correcting the abnormal cellular processing of the protein synuclein will translate into an effective treatment for multiple disorders. Because of these unprecedented scientific opportunities and pressing clinical needs, the NIH initiated a series of planning efforts to hasten discoveries in PD research that would lead to better treatments and ultimately, a cure.

In FY2000 report language, the Senate Committee on Appropriations asked the NIH to develop a coordinated effort to take advantage of promising opportunities for PD research. In response, the National Institute of Neurological Disorders and Stroke (NINDS) held a major PD planning meeting in January 2000. This meeting included all components of the PD community: basic research scientists,

clinicians, pharmaceutical company representatives, ethicists, and the representatives of non-governmental organizations (NGOs). The participants' recommendations formed the basis of a five-year PD Research Agenda to manage opportunities in four major research areas: understanding PD; treating PD; creating new research resources; and enhancing the research process. In response to the PD Research Agenda, the NINDS and other NIH Institutes and Centers (ICs) issued more than thirty grant and contract solicitations relevant to PD, organized more than thirty workshops, funded nine targeted grant supplement programs, and established important resources to complement the investigator-initiated awards that make up the core of NIH grant programs. The scientific community responded enthusiastically to these opportunities, and as a result, the NIH invested nearly $1 billion to implement PD research from FY 2000 through FY 2004.

During the Agenda's implementation, the NIH regularly assessed progress through annual analyses and coordination of the PD research portfolio, and modified the Agenda to incorporate new opportunities. At the midpoint of the PD research Agenda, the NIH held two additional planning meetings: an Agenda Implementation Review meeting in January 2002 and a PD Coordination Summit in July 2002. The Implementation Review meeting explored progress on the Agenda and involved participants from the scientific/clinical communities and NGOs. At the Summit meeting, a smaller group of scientists and clinicians identified roadblocks that were impeding PD research within the context of world-wide PD research efforts. The Summit recommendations highlighted the scientific management efforts to overcome these roadblocks, which the NIH formulated into a Matrix of low-to-high risk (of success) and short-to-long term goals. The NIH has achieved many of the Matrix goals, including improvements in shared resources, better integration and enhancement of clinical studies at the Morris K. Udall Centers for Excellence in PD Research and other PD research centers, and acceleration of therapeutics discovery and translational research.

Development of a New PD Research Plan

When the PD Research Agenda reached the end of its five-year span, the NINDS sponsored a second PD Summit, held in June 2005. Like the PD planning meeting in 2000, it brought together academic researchers, industry scientists, clinicians, and members of NGOs to assess progress made over the last five years, and develop future directions for PD research based upon the state of the field. The NIH asked participants to assess progress in prevention and treatment research and the translation of findings into therapies in five research areas: risk

factors and prevention, cell implantation and gene therapy, pharmacological approaches, DBS, and non-motor aspects of PD. The participants generated and prioritized more than fifty specific recommendations for moving patient-oriented research forward in these areas. NIH leadership and staff considered these suggestions and priorities, along with unmet goals from previous planning efforts, and developed a three-year Plan for the Federal and non-Federal PD community. This 2006 PD Research Plan (which can be viewed at: http://www.ninds.nih.gov/funding/research/parkinsonsweb/PD_Plan_2006.htm) retained some focus areas from the original Agenda, as Summit participants agreed that many of these topical areas were important to continue to pursue, with modifications informed by advances in the field.

In addition, since the Summit meeting, sixteen NIH ICs have developed the "Neuroscience Blueprint," a framework for cooperation on cross-cutting areas of neuroscience research. The first focus area that the "Blueprint" pursued was neurodegeneration and the NIH sponsored a meeting in March 2006 to discuss goals and resources to accelerate discoveries in this area. Although this meeting considered cross-cutting aspects of neurodegeneration in general, some of the priorities are extremely relevant to the PD plan. Blueprint overlap is noted throughout the Plan, as this related planning process gives added weight to several PD priorities.

The NIH is implementing the recommendations from the Plan as rapidly as possible, and this report outlines a number of highlights of this implementation presented within the framework of the priorities listed in 2006 Plan. Some of these examples illustrate large grant initiatives or programs developed by one or more NIH ICs while others highlight individual investigator-initiated projects.

With respect to specific budget allocations for each area of the Plan, the NIH funds research and research-related activities as necessary to accomplish the Plan’s goals. In making these funding decisions, NIH relies on incoming grant applications on topics relevant to these goals, and considers advances in the field, evolving scientific opportunities, competing research priorities, resources available to the specific participating Institutes and Centers and estimates of levels of future appropriations. NIH budget estimates for PD research as a whole, which include expenditures for goals in the PD Research Plan, are outlined below:

NIH Parkinson's Disease Research Funding
($ in millions)

FY 2006	$207.7
FY 2007 (estimate)	$207.0
FY 2008 (estimate)	$205.4

An Appendix of significant advances in PD relevant to the PD Research Agenda is also provided at the end of the document, to illustrate the progress facilitated by NIH planning efforts to date.

Highlights of the Implementation of the 2006 PD Plan

Risk Factors and Prevention: Goals for Understanding Parkinson's disease

Genes and PD: Genetic Variation and Risk

It is clear from past studies of PD genetics that an individual's genetic makeup is likely to place him/her at varying levels of risk for developing PD. Some risks are conferred by the inheritance of very specific genetic mutations. For example, NIH investigators and others demonstrated several years ago that dominant mutations of the LRRK2 gene, which codes for the protein dardarin, are the most common cause of inherited PD found to date. Mutations in this gene likely account for 1-8 percent of PD cases. Other genetic mutations may increase risk for the disease, such as the mutation that causes a deficiency in glucocerebrosidase, an enzyme that breaks down a specific type of fat in the body. Individuals with the most severe manifestations of this mutation develop Gaucher disease, but one of the less-severe results of the mutation can be in increase in vulnerability to developing PD. Other people may also be at risk for PD by possessing gene variants that researchers are now just beginning to understand. Participants in the 2005 Summit recommended additional research on "control" populations (e.g., individuals without PD) to identify novel genetic variations (called single nucleotide polymorphisms, or SNPs) that may place affected individuals at risk for sporadic PD. The section below highlights a number of activities relevant to this recommendation.

As a major contribution to this effort, the NINDS has established a DNA and cell line repository, a resource that facilitates research studies on genes and biomarkers associated with PD and other parkinsonian conditions. This facility, housed at the Coriell Cell Repositories in New Jersey since 2002, maintains data, cell lines, and DNA samples. Currently, 26 investigators who are studying the

genetics of PD have contributed to the collection for a total of 3287 samples from individuals with PD. Samples and data from 1584 of these are now available to the scientific community via the repository and NIH-funded researchers have already published the results from 30 scientific studies that utilized repository samples. Topics of these studies ranged from the role of defective genes in causing PD to clinical and pathologic features of the disease.

Despite the increasing availability of genetic data, small and potentially misleading studies have hampered both the identification and the confirmation of susceptibility genes for PD at the population level. Mutations in the alpha-synuclein gene are promising candidates, but large-scale studies are needed to confirm the role of alpha-synuclein in PD across populations with sporadic disease. To address this need, NIA investigators have recently used Repository samples to conduct a broad search across all genes for common variations that may contribute to sporadic PD. To date, they have provided more than 200 million data points to the scientific community, the largest collection of freely available raw genotype (i.e., genetic makeup) data on North American Caucasian PD patients. These data are all freely available via the Repository website. The development of this public, genome-wide data constitutes one of the initial contributions to a larger NIH database called "dbGaP," which will archive and distribute data linking genotypes and phenotypes (i.e., observable traits, diseases, etc.) across many health conditions. The availability of these data should facilitate the discovery of additional genetic mutations and variations that contribute to PD – and subsequently to the discovery of additional disease mechanisms and therapeutic targets. The National Institute of Environmental Health Sciences (NIEHS), NINDS, and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) have also provided support for an analysis which explored whether variability in regulatory sequences of a specific alpha synuclein gene (called SNCA) are associated with PD susceptibility. Eighteen sites from a global genetics consortium, including investigators from several NIEHS-funded studies have found strong support for the role of genetic variability in these regulatory regions in the risk of PD. Although additional studies have not yet duplicated this finding, both of these investments illustrate the importance of this goal and of population-based genetics research on PD.

Basic research studies of the cellular mechanisms of PD can also inform clinical studies of genetic variation and risk. As just one example, a cellular transport mechanism inside dopamine neurons sequesters dopamine and specific environmental toxicants and may protect against harmful effects of excess levels of these compounds. The NIEHS recently found that genetic variability in a regulatory region of this transporter gene influences the risk of PD. Specifically,

some variations that increased the level or function of the transporter reduced the risk of PD, although this effect was observed only in women.

Gene Function

In addition to clinical studies of genetics, Summit participants also recommended additional studies of the function of genes linked to PD. Many NINDS and National Institute on Aging (NIA)-supported researchers are already involved in this research, including intramural investigators at the NIH. Extramural researchers continue to contribute to this goal as well. For example, the NIA recently made a career award to an investigator who is using a fruit fly model of PD to further define the genetic changes that occur during aging which might be involved in neurodegeneration. Findings from this study may result in the identification of fundamental mechanisms of neuronal loss and could reveal potential novel therapeutic targets for human disease.

Gene Therapy and Cell Implantation: Goals for Translating Discoveries into PD Therapeutics

As mentioned in a previous section, a large proportion of dopamine neurons are lost in PD. Restoration of dopamine levels through the use of gene therapy was one therapeutic option discussed at the 2005 Summit. Replacement of the lost neurons through cell implantation or by stimulating the brain itself to generate new cells also has considerable potential for reversing this loss. To this end, participants at the 2005 Summit believed that stimulating research on understanding how dopamine neurons develop would facilitate the production of cells that could be used for transplantation should be a priority goal in the 2006 Plan.

Controlling Development of Dopamine Neurons

As just one example of NIH research is addressing this goal, NINDS-funded investigators have explored the signals that might stimulate the brain's internal repair systems, specifically those in regions affected by PD. They utilized a drug compound known to activate a specific type of dopamine receptor (the "D3" receptor), which other researchers have found plays a role in neuronal development and in the proliferation and maturation of some populations of neurons. This group demonstrated that stimulation of the D3 receptor led to proliferation of neurons in the substantia nigra – a brain region depleted of dopamine neurons in PD – and the maturation of many of these cells into

dopamine neurons. Motor function also improved in treated animals with induced parkinsonism, along a time course consistent with the new cells playing a role in recovery. Importantly, this behavioral recovery lasted at least four months past the end of the treatment. Given that some drugs that stimulate the D3 receptor are already in use for treating PD patients, the potential role of this therapeutic approach in repairing the nervous system is promising.

Numerous other NIH-supported researchers are also exploring how to promote the maturation of federally-approved human embryonic stem cell lines and animal stem cells into dopamine neurons and to stimulate the outgrowth of these cells. However, successful use of transplanted neurons derived from these cells is still limited by the occurrence of unrestrained tumor-like growth in some cases.

To facilitate this research across the stem cell community, the NIH established a Stem Cell Characterization Unit in April 2003, to address issues related to distribution of the federally-approved cell lines and the testing and use of these cells. Unit investigators recently published a paper outlining laboratory techniques to maintain many of the federally-approved lines without exposing the cultures to mouse cells, a challenge in the development of stem cell therapeutics. In addition, the NIH also began supporting a National Stem Cell Bank at the WiCell Research Institute in Wisconsin in October 2005. This bank is consolidating many of the federally funded eligible human ES cell lines in one location, reducing the costs that researchers have to pay for the cells, and maintaining quality control over the cells. The Bank is also providing technical support that will make it easier for scientists to obtain the cell lines currently listed on the NIH Human Embryonic Stem Cell Registry.

Pharmacological Approaches: Goals for Drug Discovery in PD

Animal Model Development

In addition to the invasive therapeutic approaches discussed above, improvements in pharmacological or drug therapy are of obvious interest to the PD research and patient communities. Among the many different directions that this research can take, participants at the 2005 Summit believed that the continued development of animal models that are predictive of human PD with respect to progression of disease and response to treatment should remain a high priority for the research community.

Many investigators funded by the NIH are actively exploring ways to improve animal models of PD, using manipulation of genes, exposure to environmental agents, and alteration of cellular and molecular pathways inside regions of the brain affected by PD. As an example which illustrates the diversity of the approaches used by these researchers, the National Center for Complementary and Alternative Medicine (NCCAM) is supporting an exploratory/developmental research project designed to refine a PD model in Rhesus monkey to test a natural therapy – the Ayurvedic herb Mucuna pruriens – for prevention and reduction of PD-like dyskinesias, disabling and involuntary movements that often accompany the use of PD medications.

Validation of Drug Targets

A new priority identified by the Summit participants for the 2006 Plan was the validation of drug targets for PD. Typically a goal pursued by pharmaceutical companies more often than academic researchers, target validation involves confirmation that interference with a particular cellular process can be used as an approach for treating PD.

As just one example of the type of research that facilitates the identification and validation of drug targets, NIA investigators have demonstrated that dardarin (the protein product of a recently-discovered gene for sporadic PD) is toxic to neurons. Turning off the active part of the gene prevents toxicity, demonstrating that the development of drug-like molecules that occupy the active site of the protein may be a novel and safe way to treat PD. NIA investigators also have developed and implemented a new approach for the discovery of therapeutic agents, which entraps tissues and cell fragments in a specially-designed system. This technique opens up many new avenues for identifying novel drugs to treat neurodegenerative diseases. It has already been used in the discovery of new drugs to treat congestive heart failure, and may prove particularly useful in the discovery of new treatments for nervous system diseases, including PD.

Treatment Delivery

While an advantage of drug therapies for PD is that they can be less invasive than many other treatment approaches, it is still difficult to ensure that these compounds reach the parts of the brain that are compromised by the disease. Summit participants emphasized that the development of better therapeutic delivery approaches should become a new priority in the 2006 Plan.

In October 2006, sixteen NIH Institutes, Centers and Offices directly addressed this need by releasing a grant solicitation focused on "Therapeutics Delivery for Neurodegenerative Diseases (R21)" as part of the Neuroscience Blueprint. The goal of this broad solicitation was to help researchers overcome major barriers to therapeutics delivery including drug design, drug activity and breakdown in the body, and penetration of the blood brain barrier. The development of therapeutic agents and delivery systems for neurodegenerative diseases could serve multiple needs, including implementation of novel therapies from emerging technologies to target delivery methods for the nervous system; the incorporation of new approaches from other fields such as bioengineering and tissue and cell engineering; the validation of the delivery of therapeutic agents across the blood-brain and tissue barriers to specific cell populations; and the facilitation of interactions among multidisciplinary teams to develop new approaches to drug delivery systems. Grant applications received under this solicitation are currently under review.

Drug delivery systems – for example, those used for the delivery of glial cell-derived neurotrophic factor (GDNF) – have been a controversial subject in the clinical research community. Some investigators believe that differences in delivery systems have contributed to the failure of recent GDNF trials. A research team in the intramural program at NINDS has long studied the use of convection-enhanced delivery, a technique in which constant pressure is used to deliver drugs widely in the brain. This group has already demonstrated success in a number of animal disease models (including brain tumors and PD) and in clinical testing, and it believes this technique could be used to deliver a variety of drug and gene therapies to appropriate neurons in humans with PD as well.

The NCCAM is also funding new approaches to developing therapies that may include novel approaches to delivery. Specifically, they have provided support for an exploratory/developmental grant designed to test whether a non-invasive technique called near infrared light emitting diode (NIR-LED) photobiomodulation (a form of low-intensity external light therapy) in mouse models of PD can delay symptoms of PD or limit them once they are present. Some data already suggest that NIR therapy can accelerate wound and retinal healing. Defective energy metabolism in specific neural cells may contribute to PD progression and therapies like NIR-LED hold promise for increasing energy metabolism and attenuating PD symptoms.

Translational Research

Improving successful drug discovery efforts will also require translational research, or research that bridges basic findings with clinical trials. These studies often involve the exploration of potential therapies in animal models of PD, and Summit participants indicated that this type of research should be a priority highlighted in the 2006 PD Plan.

At the time that the NIH released its Plan, it already supported a number of translational research projects targeted to PD. For example, the NINDS has provided funding for many PD grants through a broad program for translational research that includes support for large, collaborative studies, smaller exploratory/developmental grants, and training awards. The NINDS also has developed a translational research oversight committee and working group to facilitate programs and planning for this area across the Institute.

The NIA, along with the National Institute of Mental Health (NIMH), the NIAAA, and the National Institute on Drug Abuse (NIDA), has also co-sponsored a recent grant solicitation entitled "Drug Discovery for Nervous System Disorders," which is designed to stimulate the translation of basic science findings into the conceptualization, discovery, and evaluation of innovative therapeutics for central nervous system disorders, with the goal of accelerating the development of new treatments.

Pharmacological Approaches: Goals for Treating PD

Biomarkers

The NINDS and many other ICs have long recognized that the lack of biological markers of disease risk, activity, progression and response to treatment presents a significant roadblock to the advancement of therapies for neurodegenerative diseases. The Summit participants recognized this need and identified the development of PD biomarkers as a very high priority for the 2006 Plan.

In October 2006, the NIH ICs participating in the Neuroscience Blueprint addressed this recommendation by issuing a grant solicitation to encourage research on biomarkers for neurodegenerative diseases, as part of the overall NIH Blueprint for Neuroscience Research program. Although many topics related to biomarkers were highlighted in this solicitation, the NIH hopes that some of the studies funded will identify biomarkers that are consistent across species. This

consistency will help facilitate the preclinical assessment of therapeutics. This solicitation elicited a vigorous response from the research community and the grant applications are currently under review.

As an example of specific NIH contributions toward biomarker development, NIA, NIEHS, and NINDS-funded investigators have recently employed a novel method of assessing proteins to compare the pattern of expression of over 1500 proteins found in the cerebrospinal fluid obtained from patients with PD, AD, dementia with Lewy bodies (DLB) and healthy controls. The research team found that some groups of protein makers could distinguish AD, PD and DLB patients from each other as well as from controls with high sensitivity and specificity. Additional studies must confirm these findings in larger groups of subjects, but they suggest that identification of protein expression patterns may help in the clinical diagnosis and monitoring of disease progression of AD, PD and DLB.

The NIA has also awarded a research project grant relevant to this goal under its grant solicitation focused on "Proteomics in Aging and Age-Related Disorders." Project investigators proposed to explore the expression of proteins in the cerebrospinal fluid that are unique to PD, PD progression, and development of cognitive deficits in PD. Once they have identified these proteins, they will select a panel of unique proteins that could serve as the basis of a highly sensitive test.

Development of Disease-modifying Trials

Trials to treat PD may involve the testing of therapies for the symptoms of the disease or they can explore interventions that may delay or stop its progression. Summit participants encouraged the research community to continue disease-modifying trials of agents that seem most promising based on an improving understanding of the cellular effects of PD. They also encouraged the inclusion of research subjects with very early PD in these studies, once these individuals can be identified.

The NINDS has been committed to this goal for several years. Prior to the initiation of its Exploratory Trials in PD (NET-PD) in April 2003, the Institute undertook an extensive process of planning, infrastructure development, and rigorous review of candidate therapies. Specifically, a team of pharmacologists, clinicians, and clinical trial experts – including NINDS staff – developed specific criteria for the evaluation of potential therapies, including scientific rationale, blood-brain barrier penetration, safety and tolerability, and evidence of efficacy in animal models or humans. The team of reviewers solicited suggestions from

scientists and clinicians in academia and industry, as well as patient and foundation groups, in order to identify as many potential therapies as possible. A Steering Committee for this trial selected a small number of compounds to be evaluated in two sets of pilot studies: in Futility Study 1 (FS-1), researchers tested minocycline (an antibiotic related to tetracycline) and creatine (a common nutritional supplement that maintains cellular energy reserves). In Futility Study-TOO (FS-TOO), the same research team explored the promise of coenzyme Q10 (a health supplement and antioxidant) and GPI-1485 (a proprietary compound with growth factor properties). Forty-five sites participated in the enrollment of individuals with early, untreated PD for these studies and the research team completed recruitment ahead of schedule.

As implied by their titles, these trials were "futility studies," a specific kind of clinical trial that is designed from a statistical perspective to indicate rapidly whether future exploration of a particular intervention is prudent. They were *not* designed to test for the efficacy of any intervention, and it would be inappropriate to conclude from these findings that any drug is sufficiently promising to be used to treat individuals with PD now. Full-scale phase III trials are necessary to evaluate any drug that is not found to be futile in these studies. Decisions to fund phase III trials are based on scientific promise, along with safety, tolerability, drug availability and other ongoing clinical trials.

The NET-PD research team published the results of FS-1 and FS-TOO in March 2006 and January 2007, respectively. These results revealed that creatine was the only drug of the four to be sufficiently promising to explore further, and the NINDS is now supporting a large Phase III trial of creatine, which began subject recruitment in March 2007. The NINDS is also funding a large phase III trial of CoQ10 for PD, based on independent lines of promising pre-clinical data, and is assessing another 30 potential neuroprotective therapies for the next set of futility studies, using the rigorous selection process outlined above.

As another example of the development of therapies that will delay the progression of PD, investigators at NIEHS have investigated the neuroprotective property of drugs related to the cough suppressant dextromethorphan (DM) and have found that daily injections with these compounds protected dopaminergic neurons in regions of the brain that undergo cell loss in PD and restored DA levels to their target using two different models for PD. Of the five drugs studied, 3-hydroxymorphinan (3-HM), a breakdown product of DM, was the most potent for preventing toxin-induced dopamine neuron loss and motor symptoms. With its high efficacy and low toxicity, 3-HM may be a novel therapy for PD. Other intramural investigators at the NIEHS have reported that valproate (VPA), a mood

stabilizer and antiepileptic drug, also increases the expression of growth-promoting factors from astrocytes. These effects may play a major role in mediating the ability of VPA to protect PD-affected dopamine neurons from toxicant-induced damage and suggest that VPA merits consideration for therapy in PD.

Deep Brain Stimulation: Goals for DBS

Deep brain stimulation is a symptomatic therapy for PD that delivers small electrical currents to targets with the brain circuitry that is affected by the disease. While DBS is a very promising therapeutic technique, the number of investigators involved in studying DBS and clinicians treating patient has led to the collection of clinical data in a non-standardized fashion. Moreover, researchers have conducted a limited number of trials to test the effects of DBS and some of these trials have not been designed adequately to answer the full range of clinical questions that exist about the treatment. For these reasons, Summit participants encouraged the extension of follow-up for participants in DBS clinical trials, and expansion of participant numbers and standardized procedures in future trials as priorities in the 2006 Plan.

Improvements in DBS Trials

In March 2007, the NINDS addressed some of these concerns by sponsoring a small working group meeting to discuss data elements that would comprise a DBS clinical database and reporting standards for DBS studies, with a particular emphasis on PD. The NINDS is working with the participants to develop a publication following the meeting that will serve as a guide to investigators, so that researchers in the field will be able to have a standard data set to allow for comparisons across studies.

In addition, the NINDS is developing a grant solicitation that would stimulate the development of tools to facilitate the DBS surgical process, programming, and outcome assessments; and technological innovation in the design of the electrical stimulators used in applying DBS. The tools and technology produced by this program will permit enhanced targeting and delivery of therapeutic stimulation in the brain, ultimately improving the quality of life for DBS patients with movement disorders. Importantly, the tools and technology that researchers will develop in this program may improve patients' experiences during pre-surgical evaluation, surgical procedure, and/or post-surgical follow-up.

Investigators supported by the National Institute on Deafness and Other Communication Disorders (NIDCD) are also examining the relationship between cortical and sub-cortical brain areas during speech production in individuals with PD with or without DBS. Preliminary results are encouraging and suggest means of optimizing settings to improve speech performance for DBS patients.

Non-Motor Aspects of PD: Goals for Treating Non-Motor Symptoms

Clinical Studies of Non-motor Features

Participants at the 2005 Summit clearly made further exploration of the non-motor aspects of PD – which can include sleep abnormalities, fatigue, behavioral and cognitive impairments, anxiety, and depression – a major priority of the 2006 PD Plan. As just one example, they strongly recommended an incorporation of non-motor manifestations of PD into more clinical trials. The NET-PD study will address this need directly, by exploring the ability of creatine to improve some of the non-motor features of PD, in addition to its ability to slow the progression of the motor symptoms.

Improved Testing of Non-motor Features

Participants also noted that better tests for these manifestations are needed, so that clinicians can identify each patient's unique set of problems and try to resolve them. The NIH has already made significant efforts to manage this problem; several examples are highlighted below.

As mentioned above, many non-motor features accompany PD, including cognitive disturbances and in some cases, psychosis. Psychosis is particularly troublesome for patients and families; it causes a range of problems in the care of a PD patient and predicts a poor prognosis regarding both nursing home placement and death. In the past, clinicians have not had definitive diagnostic criteria for psychosis associated with PD, which is a significant roadblock to clinical researchers in testing potential therapies. To address this problem directly, the NINDS and NIMH sponsored a workshop of clinicians and researchers in November 2005 to explore the data in support of a distinct psychosis that is associated with PD and if appropriate, to begin development of diagnostic criteria for this condition. Meeting discussions, supplemented with a literature review, confirmed not only that PD psychosis has distinct clinical features but that it may occur as part of the disease process. Participants

published their findings, including provisional criteria for diagnosing psychosis associated with PD, in January 2007.

Depression is also a significant problem for PD patients, affecting up to half of all individuals with PD. However, clinicians often fail to diagnose or treat depression adequately and it is not known whether this condition is identical to the major depression observed in non-PD patients. To address this problem, the NIMH is supporting a study to examine the optimal methods to detect depression in patients with PD. The primary aim of the study is to compare and evaluate existing depression assessment tools to identify depressive disorders in PD patients and to establish the reliability and validity of these assessments for detecting persistent symptoms. The NIMH also joined the NINDS in sponsoring a workshop on the development of diagnostic criteria for PD-related depression; this meeting resulted in the publication of provisional criteria for diagnosis in 2006.

The NIMH is also supporting a project to conduct depression screening and assessment in two PD specialty care settings. The goal of this project is to determine demographic, psychiatric, neurological, and cognitive markers of depression and to develop modified criteria for affective disorders (e.g. depression, anxiety disorder, and bipolar disorder) within the context of PD. In addition, researchers are conducting an open-label antidepressant drug study to determine treatment responses under these different diagnostic criteria.

The NCCAM is funding a phase II clinical trial of the biological compound and nutritional supplement S-adenosyl methionine (SAM-e) for treatment of depression in PD. Specifically, the trial investigators are exploring whether PD patients with depression fall into differing groups as their preliminary data suggest, and are trying to improve scales to measure types of depressive symptoms in PD. NCCAM is also supporting a small trial to test whether the herb valerian can lessen sleep disorders in individuals with PD.

Previous studies have established that short term memory and attention is also perturbed in individuals with PD. The NIMH supports a study to refine the understanding of these cognitive deficits in PD patients. This research could lead to the development of a sensitive behavioral test on cognitive measures that could be used as an early detector of PD.

Understanding the Non-motor Features

In addition to improving management of these features clinically, Summit participants believed that understanding these features should be a priority of the 2006 Plan. It is likely that improving knowledge about how these effects arise will inform the development of better treatments.

As one example of efforts to address this need, the NINDS, NIA, and the National Institute of Nursing Research (NINR) have re-issued several grant solicitations over the past two years to encourage applications on the cognitive effects of PD. Projects on a broad range of research topics, from studies of the cellular and molecular mechanisms underlying cognitive changes to the development of tools that clinicians could use to assess these changes, would be appropriate for this program. The research community has responded with a number of grant applications; these applications are currently under review for potential funding.

The NIMH also supports an Advanced Center for Services and Intervention Research that conducts research on the development, evaluation, and dissemination of interventions for depression and related disorders for older adults. One project within this center examines the prevalence and co-occurrence of common psychiatric disorders in PD patients (including depression, anxiety, psychosis, and cognitive impairment). Other studies focus on modifying cognitive behavioral therapy to treat depression associated with PD. The center also supports functional imaging studies to examine aspects of treatment response.

In response to a 2005 grant solicitation entitled "Collaborative Research on Mental and Neurological Disorders," the NIMH and NINDS have co-funded a study to elucidate the neural basis of depression in PD patients. By elucidating some of the brain pathways underlying depression in PD it may be possible to compare PD-related depression to major depression in the general population. Moreover, the investigation will examine whether PD medications have therapeutic benefits for depression.

As mentioned earlier in the report, a primary cause of motor dysfunction in PD is a lack of the neurotransmitter dopamine in a set of critical brain circuits. Dopamine also plays a crucial role in modulating the brain circuits involved in working memory (a type of short-term memory) and procedural learning (e.g., learning to ride a bike). Deficits in these brain circuits may be the basis for the cognitive dysfunction observed in PD. The NIMH supports a project that is investigating the role of dopamine in working memory and procedural learning in

patients with PD using a combination of behavioral tasks and brain imaging techniques.

The NIA co-sponsors several program announcements involving non-motor symptoms of PD. These trans-NIH research initiatives seek to further understand the underlying neurobiological mechanisms associated with the cognitive impairment in PD as well as the role of neuroinflammation and neuroimmune activation in the etiology of a variety of neurological disorders including PD.

In addition to the non-motor features of PD, speech and swallowing deficits can also accompany Parkinson's. Although these are both motor functions, they often are not responsive to standard dopaminergic therapies. The NIDCD research portfolio in PD spans both of these research areas, and includes research designed to improve the voice, speech and swallowing abilities of affected individuals. Recent work has focused on expanding behavioral speech interventions to computer-assisted technology and the use of virtual therapies. A randomized study of two behavioral interventions to reduce aspiration during swallowing in individuals with PD was completed in 2006 and publication of results is ongoing. Research is also underway to develop a Sniff Magnitude Test to determine an individual's loss of smell. This test may be of value in diagnosing individuals with neurodegenerative disorders such as PD.

Tools and Resources: Goals

Brain Banks

The availability of brain tissue from individuals affected by PD is a critical need among researchers. Brain banks exist at several institutions already, but the Summit participants encouraged greater efforts at banking specimens in the 2006 Plan.

The NINDS is currently funding PD brain banks at the Mayo Clinic in Jacksonville and at Johns Hopkins University, as part of the Udall Centers program. The NINDS has recently added a new brain bank to the network, through the funding of a new Udall Center at the University of PA. The Institute anticipates expanding these banks in the future as it continues to grow the program. The Parkinson's Disease Data Organizing Center (PD-DOC; which is coordinating all of the clinical data collection across the Udall Centers) has also developed a minimum data set for neuropathology data collection and procedures for use by all PD researchers. The Parkinson's Disease Foundation (PDF) is

interested in partnering with NINDS to support this work and it is currently looking for collaborative opportunities.

The NIMH supports the Harvard Brain and Tissue Resource Center, which is among one of the most comprehensive postmortem brain collections for neurological and psychopathological disorders (including PD). Investigators may apply for and obtain tissue specimens or genetic material to study a host of research questions.

In addition to these examples, numerous other brain banks around the country also collect and distribute samples of tissue from individuals PD; the NINDS provides a comprehensive list of these resources on its website at: http://www.ninds.nih.gov/funding/research/parkinsonsweb/brainbanks.htm.

Updates in Other Areas of Research

Exploring the Role of the Environment in PD

The NIEHS continues to lead the NIH effort in understanding the role of the environment in the risk of PD. As part of this ongoing effort, the Institute has launched a new initiative to support Centers for Neurodegeneration Science. This new initiative will build on the success of the existing Collaborative Centers for Parkinson's Disease Environmental Research Program, broadening the scope to include other environmentally-mediated neurodegenerative disease and allow greater opportunities for investigators to identify common mechanisms that may underlie neurodegenerative processes in PD and related disorders.

The NIEHS also continues its research on environmental exposures and PD risk. The Institute recently awarded a new grant to the University of Washington to conduct a large cohort study to determine whether the prevalence of PD is increased in shipyard welders relative to a non-welder reference group. The research team being assembled for this new study has developed a rigorous study design that incorporates the efforts of movement disorders specialists, epidemiologists, industrial hygienists, and industry leaders. The results of this study could have significant public health impact, as the demonstration of a positive relationship between welding and PD would suggest that many cases could be prevented through worksite modifications to reduce exposures.

Iron elevation is well-documented in some brain regions affected by PD but its cause and contribution to subsequent neurodegeneration remain unknown.

NINDS-supported investigators at the Buck Institute for Aging (in Novato, CA) used mice to study the consequences of administration of iron in early life, a time period of peak transport of iron into the brain. Mice administered iron at doses equivalent to those found in iron-fortified human infant formula during a developmental period equivalent to the first human year of life displayed progressive midbrain neurodegeneration and enhanced vulnerability to toxic injury. This may have major implications for the impact of neonatal iron intake as a potential risk factor for later development of PD and suggests that epidemiology studies may benefit from a consideration of early life exposures.

The NIEHS has also awarded a grant to investigators at UC-Davis to study a PD registry in Denmark and use it to conduct the largest, population-based, case-control study every attempted. The investigators will examine lifetime occupations, exposures to solvents and pesticides, drugs and medications, along with the influence of genetic variability. The large sample size in this study will provide unprecedented power for answering many of the unknown questions regarding PD genetic and environmental risk factors.

Understanding the Biology of PD

One of the fundamental contributions of NIH-supported research to PD is an improved understanding of the cellular and molecular causes of disease. For example, NIEHS and NIA-funded investigators have measured specific patterns in the protein production of mitochondria – the energy generators of the cell – in the substantia nigra of PD patients to those from age-matched controls. They identified mortalin, a protein involved in mitochondrial stress, as a protein that is substantially decreased in PD brains as well as in a cellular model of PD. Nine proteins that bind to mortalin were also identified as potential mediators of PD pathology. These findings provide novel directions for understanding the role of mitochondrial dysfunction in PD and potential targets for therapy development.

Researchers have also linked mutations in the human parkin gene to familial and some sporadic cases of PD. Researchers supported by NINDS, NIA, NIMH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and NIEHS recently reported that expression of mutant but not normal human parkin in fruit flies causes age-dependent, selective degeneration of dopamine neurons accompanied by a progressive motor impairment. Increases or decreases in the fruit fly form of a specific dopamine transport molecule partially rescues or exacerbates, respectively, the degenerative changes caused by mutant human

parkin. These results support a model in which the vulnerability of DA neurons to parkin-induced neurotoxicity results from the interaction of mutant parkin with cellular dopamine.

The protein alpha-synuclein has been linked to PD due to its appearance in an aggregated form in neurons of people with the disease. Some researchers believe that the formation of alpha-synuclein aggregates is an important factor in the development of the disease. A team of scientists at Cornell University, supported by the National Center for Research Resources (NCRR), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and NIA, used a special imaging technique called electron spin resonance spectroscopy to measure the molecular structure of the alpha-synuclein molecule. This study elucidated some of the factors that play a role in aggregation of the molecules.

Collaborations

Collaborations occur at many levels in the research community, from individual researchers from different laboratories and institutions working with one another, to collaborations across NIH ICs, between the NIH and private research funding organizations. As a particularly noteworthy example of the latter, the NINDS, NIA, NIMH, the Movement Disorder Society, the Department of Defense (DoD), and several industry sponsors contributed support to the first World Parkinson Congress held in February 2006 in Washington, D.C.. Approximately 100 international professional groups and non-profit organizations endorsed this meeting, which emerged as a recommendation at the first NIH-sponsored PD Summit in 2001. The Congress brought together, for the first time, a broad group of international research scientists, clinicians, PD patients and their caregivers. Sessions were equally broad and targeted basic science topics, clinical advances, and importantly, included many interactive workshops and sessions on living with PD. Participants viewed the meeting as a great success, and organizers hope to plan a second Congress in June 2009.

The NINDS, along with the DoD, the PDF, and two private companies, are also collaborating to fund a longitudinal cohort study called Postcept. Postcept involves a cohort, or group, of approximately 800 Parkinson's patients and controls who have volunteered for clinical assessments, imaging, and blood draws for DNA donation over the next 3 years. This unique cohort is the largest and most contemporaneous since the NINDS-funded DATATOP trial more than a decade ago. This cohort will be studied in the hopes of identifying the earliest

symptoms of PD, potential biomarkers of PD, and environmental or genetic risk factors.

The NIEHS is supporting the work of a PD Epidemiology Study Group to develop a set of standard questionnaires that can be administered to subjects enrolled in clinical and/or epidemiology PD studies. These will be made available both in the US and internationally to help investigators use similar methods for collecting information about different risk factors (e.g., medical history, occupation, lifestyle). The use of a uniform questionnaire will simplify pooling of data and comparison of results across studies. The NIEHS-supported PD Epidemiology Study group members are exploring a partnership with the Movement Disorders Society to aid in the possible translation of the questionnaire into other languages.

The NIEHS, together with the Michael J. Fox Foundation, is also providing funds to support the planning and conduct of a pilot study for a California statewide registry of PD. This registry will answer many basic questions about PD such as how many individuals are affected, their age, sex, and geographic distribution, and whether the disease is increasing or decreasing over time. In turn, this information will provide important clues for scientists studying the causes of PD. Many reasons make California an ideal state for a registry -- it has a large population, is culturally, geographically and economically diverse and has been a leader in environmental surveillance.

The NINDS-funded PD-DOC is developing a collaboration with the Parkinson's Action Network to post lay summaries of the research being conducted by the Udall Centers for Excellence, as well as other NINDS-funded basic, translational, or clinical studies in PD on a central website. The summaries would include not only basic information about the research project but would also provide comments on the significance of the study results (once available) to public health.

Next Steps in PD Planning

Although the NIH is engaged in many activities that address goals outlined in the 2006 PD Research Plan, additional research topics warrant closer scrutiny in our future planning efforts. The NINDS expects to target several of these topics – *biomarkers, outcome measures, and the facilitation of clinical trials* – at a focused planning workshop, to be held in September 2007. This meeting will also explore lessons learned from past clinical trials, early indicators of PD and early

diagnoses, and the use of animal models and developments in technology to advance these research areas. It is expected that recommendations from this 2007 meeting will help the NIH expand and update its 2006 Plan and provide additional goals that will facilitate the translation of research into the clinic and the design of the clinical trials themselves.

Conclusions

PD research, like many other research areas, is in a constant state of flux as we understand more about what causes PD and how we can best prevent it from occurring in the first place and/or treat the disease once it is evident. For this reason, our surveillance of the field for new research goals must continue, and the NIH is committed to this task. The NIH anticipates that in the coming year, it will have many more advances to report that are relevant to the 2006 PD Plan, recruitment updates from the NET-PD Phase III trial, and additional recommendations regarding biomarkers and other clinical measures useful for facilitating translational and clinical research. PD remains a high priority for the NIH, and it will continue to be until the research community finds a way to treat PD and its associated conditions more effectively.

A - Appendix

Scientific Advances Linked to the Parkinson's Disease Research Agenda
(*Indicates those advances that were supported in part by the NIH); this information also available at:
http://www.ninds.nih.gov/funding/research/parkinsonsweb/PD_Plan_2006.htm#Appendix)

I. Understanding Parkinson's disease

Using genetics to understand Parkinson's disease

New genes discovered:

- *SNCA (PARK4; also related to the earlier discovery of PARK1, the original mutation discovered in alpha-synuclein)
- *PARK6 (PINK1; discovered through collaborative effort between European genetics and NHGRI and community.
- PARK7 (DJ-1)
- *PARK8 (LRRK2) - LRRK2 is the most common genetic cause of PD found to date, and may account for 7% of familial PD and for a significant fraction of sporadic PD cases.
- *Variations in the UCHL1 gene appear to protect against PD
- *Variations in specific, less-common genetic regions of mitochondrial DNA may be associated with a reduced risk of PD, including Complex I, a component of the mitochondria that is already known to be vulnerable to environmental toxicants
- *Variations in a gene involved in the breakdown of dopamine appear to influence the cognitive changes that can occur in people with PD; PD medications can worsen these effects
- *BDNF genetic variants are associated with onset age of familial PD.
- *Variations in the apolipoprotein E gene control the risk and age at onset of PD
- *Variations in the tau gene may confer susceptibility to PD
- *In men, the protective effect of smoking against PD appears linked to the presence of a specific variation in the MAO-A gene (involved in the breakdown of dopamine)
- The Nurr1 gene, crucial to the development of dopaminergic neurons, may also act as a risk factor for the disease.

- Variations in synphilin 1 have been associated with PD, and synphilin may play a role in the toxic aggregation of proteins, may adversely affect their degradation, and may contribute to apoptosis and formation of Lewy bodies.
- A gene involved in male differentiation during development, Sry, was found to be expressed in rat substantia nigra, and is linked to dopaminergic degeneration in male rats.
- *The NINDS repository has banked over 10K samples, (5436 from Parkinson's disease and 5271 control subjects) with known causal genes including parkin, LRRK2, and synuclein triplication. Publicly available samples and data exist at http://locus.umdnj.edu/ninds for 1351 subjects with Parkinson's disease and approximately 100 with other forms of parkinsonism. A whole genome study (SNP based analysis) is underway in the NIA intramural program using these samples in Parkinson's disease to identify risk factors for sporadic disease. The NINDS has publicly posted clinical data and a whole genome SNP analysis from this study's progress thus far, for close to 300 control subjects, which has been accessed by over 50 researchers to date.

Epidemiology to determine risk factors for Parkinson's disease

- *Chronic systemic exposure to the pesticide rotenone reproduces features of PD in an animal model
- *Rotenone produced cellular toxicity through increases in oxidative stress
- *Neurotoxicants appear to interact with one another to enhance their cellular effects
- *The nervous system may be able to survive some levels of neurotoxicant exposure unless additional environmental or genetic risk factors provide another "hit" to the system
- *Higher levels of physical activity may lower the risk of PD in men or men predisposed to PD tend to avoid strenuous physical activity in their early adult years
- *Moderate doses of caffeine may have a protective effect on the risk of developing PD in men and women
- *Postmenopausal estrogen therapy appears associated with a reduced risk of PD in women who have not had hysterectomies.
- *Women who combine hormone replacement therapy with heavy caffeine use may be more likely to develop PD
- *Even a single incident of moderate to severe head trauma may increase the risk of developing PD
- *Milk intake may be associated with an increased risk of PD
- *Welding may be linked to a higher incidence of PD

- Excessive daytime sleepiness has been linked to men who go on to develop PD.
- Life and death of neurons involved in Parkinson's disease
- *Disturbances of the ubiquitin-proteosome system may play a role in the development of hereditary and sporadic PD
- *An intermediate form of alpha-synuclein fibrils may play a key role in neurodegeneration and dopamine may stabilize this form
- *Increased expression of mutant alpha-synuclein causes abnormal cellular function
- *Alpha-synuclein may serve a protective function in PD
- *Normal parkin protein may play a role in the targeting of misfolded proteins for destruction and may also serve additional neuroprotective functions
- *Individuals with PD exhibit a reduced number of norepinephrine-producing nerve endings in the heart
- *DJ-1 and PINK-1 appear to interact via mitochondria to serve a neuroprotective function in the cell
- A novel technique enables researchers to show that one of two previously undistinguishable types of nerve cells is selectively vulnerable in PD, illustrating how brain movement control circuits malfunction, revealing the molecular mechanism that kills those cells, and identifying a potential new target for drugs to slow PD.

Neural circuits in Parkinson's disease

- FDA approved DBS for use in advanced PD
- *DBS may reduce symptoms of PD by interfering with the abnormal firing patterns of the targets of STN neurons, and not by simply silencing the STN itself
- *The beneficial effects of the Lee Silverman Voice Treatment for PD are accompanied by a normalization of brain activity in regions of the brain associated with speech control
- Calcium channels act as pacemaker cells in the nigra, and sodium channels are associated with a loss of connectivity of striatal spiny neurons in dopamine depletion PD models, suggesting potential drug targets for PD.

II. Developing New Treatments for Parkinson's Disease

Pharmacological approaches

- *Creatine is found to be a promising neuroprotective agent to test in Phase III trials for PD.

- *High-dose Coenzyme Q10 appears to slow the progression of functional loss in a phase II clinical trial
- Apomorphine, an injectable drug, is now approved for use to rapidly treat "off" periods commonly associated with long-term L-dopa use. Patients experience a return to movement within 20 minutes.
- Rasagiline, a potent MAO inhibitor, was shown to be safe and effective as monotherapy in PD and as adjunctive therapy for patients receiving levodopa; 1-year trials have suggested that rasagiline may be neuroprotective and may slow the progression of PD.
- Gambling was associated with the use of dopamine agonists, patients and clinicians are now aware of this potential side effect.
- *Vaccination with copolymer-1 appears as a promising therapeutic approach in an animal model of PD
- *COX-2 is involved in PD-related neurodegeneration, and COX-2 inhibitors appear promising in an animal model as a potential treatment for PD
- Clinical trials of glial cell line-derived neurotrophic factor (GDNF) have not shown consistent results
- *Brain images from participants in industry-funded GDNF trials do not exhibit cerebellar damage suspected based on preliminary findings in animal models
- *GDNF is effective in improving motor function in aging primates and in a primate model of PD
- *The use of nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) may delay or prevent the onset of PD.
- *Levodopa either slows the progression of Parkinson's disease or has a prolonged effect on the symptoms of the disease

Deep brain stimulation and other surgical approaches

- Unilateral pallidotomy does not produce overall neuropsychological or psychiatric changes in patients with PD.
- After a 5 year follow up, study of patients who had received DBS showed no incidence of cognitive decline.

Cell implantation

- *Fetal tissue transplants appear to have minimal beneficial effects in treating advanced PD and are accompanied by difficult-to-control dyskinesias.
- *Dopamine neurons can be developed in culture from Federally-approved human embryonic stem (ES) cells

- *Neural cells derived from human and mouse ES cells can integrate into an animal host and reduce parkinsonian symptoms; adult human stem cells (removed during therapeutic surgery) also have similar potential
- *Transplantation of dopamine nerve cells derived from somatic cell nuclear transfer can help treat parkinsonian symptoms in mice
- Human neural progenitors can deliver GDNF to parkinsonian rodents and aged primates
- *Intrastriatal implantation of human retinal pigment epithelial cells attached to microcarriers reduce motor deficits in animal models of PD and are safe and well-tolerated in humans
- Novel genes have been identified which are up- or down-regulated in survival of different types of dopaminergic neurons, suggesting a basis for selective vulnerability. These genes may also be important in the generation and survival of dopaminergic stem cells used therapeutically.

Gene therapy

- *Researchers can generate regulated viral vectors for delivering therapeutic genes for treating PD.
- *Gene transfer of interfering RNAs can reduce the expression of mutant alpha-synuclein in an animal model of PD
- *Gene therapy that combines delivery of the enzyme that synthesizes L-dopa, along with a necessary co-factor, can produce long-lasting reductions in parkinsonian behaviors in a rodent model
- *Gene therapy that delivers GDNF can prevent neurodegeneration in primate models of PD
- PET and MRI have been successfully used together in the non-invasive assessment of gene transfer and gene therapy in humans.
- Sustained, regulated expression of AAV vector proteins was shown, even in the presence of an immune response in animals, suggesting that AAV would likely be successful in humans, most of whom possess antibodies to AAV naturally.
- Preclinical studies have demonstrated that infusion of neurturin, a protein similar to GDNF, improved symptoms in primate animal models of PD within 3 months; a small pilot trial of gene therapy for neurturin has begun in 12 PD patients.
- GAD, a protein involved in synthesis of inhibitory neurotransmitter, was shown to improve PD symptoms in a rat model; a pilot trial of GAD gene therapy is being pursued in 12 PD patients. Interim results have been positive thus far, with patients showing a statistically significant improvement in

motor symptoms on the side of the body correlated with the side of the brain that received gene therapy.
- Four patients have now been treated with dopaminergic enzyme (AADC) gene therapy in an open label unblinded study; preliminary analysis at 6 months show that 3 of 4 patients improved on their motor scores.

Non Motor Aspects of PD

- Diagnostic criteria for depression in PD have been developed, and clinical scales for fatigue, as well as Activities of Daily Living (ADL) have been validated in PD patients.

Rehabilitation

- Exercise improves social interactions and physical abilities in PD patients, and studies suggest that tai chi may improve balance.
- Acupuncture is safe and well tolerated in PD; pilot studies show that it does not improve motor symptoms, but may improve non-motor symptoms and overall quality of life.
- An educational program has been developed for use by PD patients and their caregivers to address the psychosocial challenges of PD.

Outcomes research and evidence based medicine

- Practice parameters have been developed by the American Academy of Neurology for:
  - Neuroprotective and alternative therapies in PD;
  - Treatment of motor fluctuations and dyskinesias
  - Depression, psychosis and dementia
  - Diagnosis and prognosis of new onset PD
  - Initiation of treatment in PD
- Depression in PD is associated with difficulties in Activities of Daily Living (ADL) rather than motor problems.

III. Creating new research capabilities

Array technologies

- NINDS has established four Microarray Consortium centers to further basic and translational research through the acquisition and dissemination of high quality gene expression data.

Models of Parkinson's disease

- *Exposure to rotenone can be used to create a new rodent model of PD (see above), as well as fruit fly model of PD
- Transgenic and knock-out models have been created for many of the genes associated with PD to date, including synuclein, parkin, PINK1, DJ1, UCHL-1, and nurr1.
- Fly models, which offer rapid and inexpensive means to screen drugs for PD, have been created with synuclein, parkin, and DJ-1. Similarly, worm models have been created for synuclein, parkin and DJ-1.
- *Use of the combined application of the neurotoxicants paraquat and maneb can generate a rodent model of PD
- Expression of the c-terminal truncated form of alpha synuclein generates a mouse model with lewy body-like inclusions.
- *Over-expression of normal or mutant human alpha-synuclein via gene therapy can induce progressive parkinsonian neurodegeneration and motor impairment in marmosets
- *Researchers have used genetic engineering to disrupt mitochondrial function in the dopamine neurons of mice to produce a new mouse model of PD. A transgenic mouse model of synuclein has been generated which exhibits similar pathology to that seen in humans, an important preclinical animal model that may be useful for testing PD therapeutics.
- Animal models of PD can be created by using proteasomal inhibitors, implicating the involvement of this cellular process in the pathology of the disease - these models may provide a useful tool for the evaluation of therapeutics.

Biomarkers

- Levels of alpha synuclein, homocysteine, and other molecules in blood plasma may correlate with PD; studies are underway to test these finding in larger PD populations.

Neuroimaging

- *Current imaging modalities are insufficient to be used alone in diagnosing PD or as a biomarker for disease progression
- *Magnetic resonance imaging may be useful as an early marker for detecting dementia associated with PD

Brain banks and other repositories

- *1140 PD genetic samples are now available in the NINDS Human Genetics Repository for use by the research community, along with approximately 750 control samples
- *Update on Udall banks to date.

IV. Enhancing the research process

Ethical issues

- *Individuals' decisions about whether to participate in an early clinical trial of gene therapy for PD will likely depend more on their attitudes towards and tolerance to risk, their perceived benefit of science to society, and a personal tendency toward action, and not on their clinical, functional, or demographic status.
- *PD clinical researchers believe that sham surgeries should be included to show efficacy in clinical trials of neurosurgical approaches to treating PD

Innovative funding mechanisms

- The NIH continues to explore the best ways to fund research that enables the translation of basic bench findings into potential therapeutics for degenerative diseases. The Translational Neuroscience program, a milestone-driven research program, continues to receive and fund research that will provide the preclinical data necessary to submit INDs to the FDA for Parkinson's Therapeutics. Studies ongoing in the program include those on stem cells, gene therapy, and drug therapeutics for neurodegenerative diseases.

Public-private partnerships

- NIH continues to develop public private partnerships to enhance PD research, creating novel requests for applications with voluntary organizations and supporting a large international meeting on PD with the entire research, clinical, public, and private PD communities. Given that public private partnerships continue to be a priority for the Roadmap and other large NIH-wide initiatives, that activities in this area will continue to develop.